Toward new sensitive measures to evaluate gait stability in focal cerebellar lesion patients

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Abstract The evident ataxic characteristics of gait in patients with cerebellar damage suggest that the cerebellum plays an important role in the neural control of gait. Ataxic features, such as increased gait variability and increased step width, are often related to gait stability. However, the link between these measures and gait stability is not straightforward. Therefore, to gain more insights into relations between gait stability, gait variability and gait ataxia, we quantified gait stability using the short-term maximum Lyapunov exponent. This is a more valid measure of gait stability, derived from dynamical systems theory. Eighteen patients with focal cerebellar lesions after tumor resection walked on an instrumented treadmill at 1.0 m/s for three minutes. The patients displayed relatively mild functional deficits ($ICARS = 6.9 \pm 6.4$, range $0 - 20$) and had a lower overground walking speed as compared to healthy controls (1.12 m/s versus 1.31 m/s). During treadmill walking, the short-term maximum Lyapunov exponent was higher in cerebellar patients, indicating reduced gait stability. Furthermore, step width was increased in the patient group while other spatio-temporal gait parameters were similar. Patients with the largest lesions in the vermis displayed the least stable gait pattern. These observations imply that the short-term maximum Lyapunov exponent is a sensitive measure of gait deficits in mildly ataxic cerebellar patients.

Highlights Gait stability was quantified using the short-term maximum Lyapunov exponent; Gait stability was reduced in mildly ataxic patients with focal cerebellar lesions; Vermal lesion size correlated with gait stability (Lyapunov exponent); Step width was increased in the patients and was correlated to ataxia severity

Key words Ataxia; cerebellum; locomotion; short-term maximum Lyapunov exponent; vermis

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1 Introduction

The evident ataxic characteristics of gait in patients with cerebellar damage suggest that the cerebellum plays an important role in the neural control of gait [for review: 1]. Prominent ataxic gait features include increased gait variability [2, 3, 4, 5, 6, 7, 8, 9, 10] and an increased step width [2, 3, 5, 8, 9]. Increased gait variability is often used to infer reduced gait stability [for review: 11] and, similarly, step width has been used as a measure of gait stability, for instance in cerebellar lesion patients [3]. In this group increased step length variability has been associated with damage in specific areas in the cerebellum, partially different from cerebellar areas related to increased lateral sway and step width [3, 4]. These observations are important since the individual contributions of balance and limb-coordination deficits to ataxic gait are still under debate [2, 12]. Furthermore, increased gait variability, specifically during slow walking, has been linked to fall risk in cerebellar ataxia patients [7].

However, the link between gait variability and gait stability is not straightforward. From a biomechanical perspective, increased variability itself does not necessarily imply decreased stability, since stability depends on both the constraints and the control strategy of a system (for discussion, see [11]). This notion is important since in cerebellar patients increased gait variability could be related to cerebellar deficits in intra-limb coordination [2], rather than to gait stability.

Likewise, step width is also not an ideal measure to quantify gait stability. In order not to fall, the center of mass needs to be controlled such that it stays over the base of support. For dynamic conditions, such as gait, this is best assessed using the extrapolated center of mass concept [13]. The extrapolated center of mass combines center of mass position and velocity, and it should be within the base of support [11, 13]. Because the distance between the extrapolated center of mass and the boundary of the base of support (the 'margin of stability'), is not only affected by step width but also by movements of the rest of the body, it is clear that an increased step width does not necessarily imply more stability.

A more valid [11] measure for gait stability is the short-term maximum Lyapunov exponent [14], derived from dynamical systems theory. This measure quantifies the ability to recover from small perturbations. It has a valid theoretical basis and has been shown to have a high predictive validity with respect to falling in both modeling and observational studies [for review: 11]. While this measure has been used to evaluate gait stability in many different populations such as elderly [15, 16], amputees [17, 18] and patients with knee osteoarthritis [19], anterior cruciate ligament deficiency [20] and peripheral neuropathy [21], so far it has, to the best of our knowledge, not been used to evaluate gait stability in cerebellar ataxia patients.

Here, we aimed to gain more insight into relations between gait stability, gait variability and gait ataxia. Therefore, we assessed gait stability and variability in a group of patients with focal cerebellar lesions after tumor resection. We specifically focused on stability in the medio-lateral direction in these mildly ataxic cerebellar patients, inspired by the commonly observed increased step width in cerebellar ataxia. We quantified gait stability using the short-term maximum Lyapunov exponent [11, 14] and we evaluated the margin of stability based on the extrapolated center of mass [13]. We hypothesized that patients would walk with a less stable gait pattern and with a reduced margin of stability. Specifically, we expected that the short-term maximum Lyapunov exponent would make an important contribution to the description of gait deficits in this mildly ataxic patient group.

2 Materials and methods

2.1 Participants & Protocol

Eighteen cerebellar patients (age: 24.4 ± 7.3 yrs; $mean \pm SD$; 13 female, 5 male) and fourteen healthy participants (24.4 ± 3.5; 11 female, 3 male) participated in the study. All patients displayed chronic focal lesions after cerebellar tumor resection (various types, see Table 1). Nine patients received radiation therapy and four of them chemotherapy (Table 1). Lesion sizes are summarized in Table 1 (more details on lesion locations and on magnetic resonance imaging data acquisition and analysis procedures can be found in the supplementary materials). All patients were in a stable condition (> 2 years post-op; range $4.8 - 30.2$ yrs; Table 1). Severity of ataxia was rated using the International Cooperative Ataxia Rating Scale [ICARS; 22]. All participants gave written informed consent, as approved by the local ethics committee and in accordance with the Declaration of Helsinki.

Participants performed three trials of overground

Table 1: **All patients had stable focal lesions after cerebellar tumor resection**

#	Age (years)	Time Post-op (years)	Sex	Diagnosis	Lesion Volume (cm^3)	Vermal Lesion Volume (cm^3)	ICARS Total /100	ICARS P&G /34	ICARS Kin Fun /52	Adjuvant Therapies Radiation	Adjuvant Therapies Chemo
1	28.8	13.9	f	Lhermitte Duclos Disease	58.0	-	3	1	1	-	-
2	20.2	8.7	f	Pilocytic Astrocytoma	8.2	-	3	0	0	-	-
3	18.1	6.5	f	Pilocytic Astrocytoma	4.5	-	1	0	1	-	-
4	19.6	11.8	m	Pilocytic Astrocytoma	1.7	1.1	6	3	2	-	-
5	20.5	4.8	f	Pilocytic Astrocytoma	47.3	5.6	3	1	1	-	-
6	20.5	13.1	f	Pilocytic Astrocytoma	36.3	-	2	1	0	-	-
7	19.0	13.2	m	Pilocytic Astrocytoma	15.7	-	7	2	5	-	-
8	41.2	28.1	f	Pilocytic Astrocytoma	20.2	4.9	20	6	10	Y	-
9	26.9	24.9	f	Pilocytic Astrocytoma	58.4	-	5	1	1	Y	-
10	22.0	18.7	m	Astrocytoma grade II	2.0	0.7	1	0	1	-	-
11	21.6	19.5	f	Astrocytoma grade II	7.1	2.1	0	0	0	Y	-
12	31.4	19.7	f	Astrocytoma grade III	8.6	0.4	11	5	4	Y	-
13	22.3	17.7	m	Medulloblastoma	22.0	3.3	13	6	2	Y	-
14	18.6	13.6	m	Medulloblastoma	6.3	2.5	19	5	10	Y	Y
15	18.4	15.5	f	Medulloblastoma	5.4	2.2	5	1	3	Y	Y
16	31.3	18.2	f	Medulloblastoma	14.2	4.0	17	10	4	Y	Y
17	18.5	10.0	f	Medulloblastoma	22.6	5.2	2	1	1	Y	Y
18	39.9	30.2	f	Hemangioblastoma	no MRI	no MRI	6	4	2	-	-

For patient 18 no MRI data was acquired. ICARS = International Cooperative Ataxia Rating Scale [22]; P&G = Posture & Gait sub-score; Kin Fin = Kinetic Functions sub-score; f = female, m = male; Y = yes.

walking at self-selected speed over a distance of 6 m [23], followed by three minutes of treadmill walking at 1.0 m/s. In daily life none of the participants employed walking aids and all testing was performed without walking aids or holding the hand rail of the treadmill. We recorded three-dimensional kinematics at 100 samples/s (Vicon Nexus, Oxford Metrics, Oxford, UK) using a marker cluster placed at the pelvis. During treadmill walking 3D ground reaction forces were collected at 1000 samples/s (custom built instrumented treadmill, Forcelink, Culemborg, The Netherlands).

2.2 Data analysis

We calculated overground walking speed as the mean forward velocity of the pelvis marker cluster during the three overground walking trials. We calculated gait stability for the treadmill walking trials. Heel strike and toe-off events were extracted from the center of pressure trajectory [24]. Gait parameters were based on 150 strides for each participant. Step width was defined as the medio-lateral distance between the average center of pressure locations during subsequent single stance phases. The coefficient of variance of stride time was calculated to assess stride time variability.

Gait stability was addressed by calculating the short-term maximum Lyapunov exponent (λ_S) from the medio-lateral displacement of pelvis marker cluster, following Bruijn's protocol [25]. In short, the Euclidean distance between each data point in state space and its nearest neighbor was tracked over time. A divergence curve was constructed by taking the mean of the log of all these time-distance curves. The short-term maximum Lyapunov exponent is the slope of this divergence curve over $0 - 0.5$ strides. Higher values for λ_S imply less gait stability [14, 25].

Additionally, we calculated the 'margin of stability' between the 'extrapolated center of mass' and the medio-lateral base of support [13]. To calculate the 'extrapolated center of mass' we estimated the center of mass and its velocity from the center of pressure trajectory. The margin of stability quantifies how close an inverted pendulum model of the participant would be from falling sideways. Therefore, a greater margin is associated to more stable gait.

2.3 Statistical analyses

We used Student's t-tests to compare gait parameters between groups. Correlations between specific gait parameters, ICARS (sub) scores and lesion measures were evaluated within the patient group using Pearson regression analysis. Analyses were performed with MATLAB (The MathWorks, Inc, Natick, MA) and a traditional level of significance ($\alpha = 0.05$) was used.

3 Results

The cerebellar patients displayed relatively mild functional deficits ($ICARS = 6.9 \pm 6.4$, range $0 - 20$; Table 1) and self-selected a lower overground walking speed as compared to healthy controls (1.12 ± 0.12 m/s vs. 1.31 ± 0.17 m/s; $p = 0.001$; Table 2. When gait characteristics of both patients and healthy controls were compared at an equal speed of 1.0 m/s during treadmill walking, most gait parameters were similar (Table 2). However, the maximum short-term Lyapunov exponent was higher in the patient group; hence their gait pattern was less stable than that of the healthy controls. Mean step width was also significantly higher in the patient group (0.21 ± 0.03 m) than in the control group (0.19 ± 0.02 m; $p = 0.046$).

As group differences were observed for self-selected overground walking speed, λ_S, and step width, we evaluated how these measures correlated with clinical outcome measures as ICARS (sub) scores and (vermal) lesion sizes. From these measures only step width was significantly correlated to total ICARS score ($r = 0.57$; $p = 0.014$; Fig. 1). In addition, correlation between the Posture and Gait sub score and the Kinetic Function sub score on the one hand and step width on the other was comparable ($r = 0.53$ and $r = 0.54$, respectively). Furthermore, λ_S appeared correlated to Posture and Gait sub score, but this was just below significance level ($r = 0.46$; $p = 0.053$; Fig. 1). Finally, none of the parameters were significantly correlated to lesion size ($|r| < 0.4$; $p > 0.1$ for all), but within the patients with vermal lesions ($n = 11$; Table 1) the vermal lesion size was positively correlated to λ_S ($r = 0.64$; $p = 0.033$; Fig. 1). This indicates that the patients with the largest vermal lesions were the ones with the highest λ_S, i.e. lowest gait stability.

In order to address relations between different gait measures, we evaluated correlation between self-selected overground walking speed, stride time variability, λ_S, step width and margin of stability within the patient group. Margin of stability and step width were strongly correlated ($r = 0.96$; $p < 0.001$; Fig. 2). In addition, stride time variability was significantly correlated to λ_S ($r = 0.51$; $p = 0.031$; Fig. 2). None of the other correlations reached significance ($r = 0.44$; $p = 0.07$ for stride time variability vs. margin of stability; $|r| < 0.4$; $p > 0.1$ for all others).

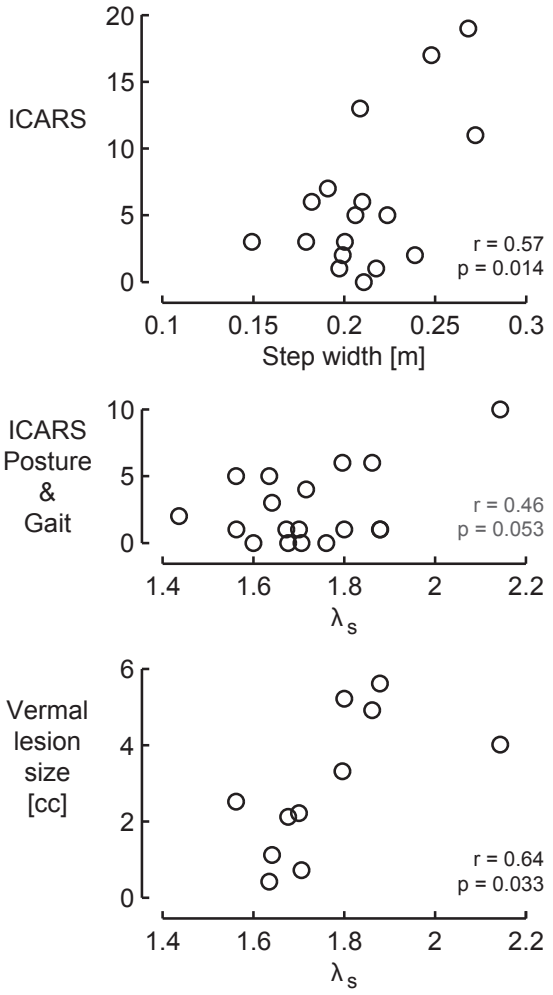

Figure 1: **Step width and gait stability are correlated with clinical measures. A)** Step width was correlated to total ICARS score (International Cooperative Ataxia Rating Scale [22]). **B)** Correlation between the short-term maximum Lyapunov exponent (λ_S) and the ICARS sub score for Posture & Gait was not significant ($p = 0.053$). **C)** Short-term maximum Lyapunov exponent (λ_S) values for the patient subgroup with vermal lesions versus the size of the lesion. Vermal lesion size was positively correlated to λ_S, indicating that the patients with the largest vermal lesions were the ones with the lowest gait stability.

Table 2: **Cerebellar patients walk with reduced dynamic stability and wider steps**

	Patients	Healthy Controls	
	Mean ± sd	Mean ± sd	p-value
Self-selected overground walking speed [m/s]	1.12 ± 0.12	1.31 ± 0.17	**0.001**
Stride time [s]	1.11 ± 0.06	1.11 ± 0.05	0.91
Stance time [%]	64.72 ± 0.76	64.78 ± 0.73	0.83
Double support time [%]	15.06 ± 0.67	15.30 ± 0.67	0.31
Stride time variability [%]	2.56 ± 0.72	2.18 ± 0.67	0.14
Maximum Lyapunov exponent	1.72 ± 0.16	1.58 ± 0.14	**0.011**
Step width [m]	0.21 ± 0.03	0.19 ± 0.02	**0.046**
Margin of stability [mm]	82.6 ± 12.9	75.1 ± 10.4	0.08

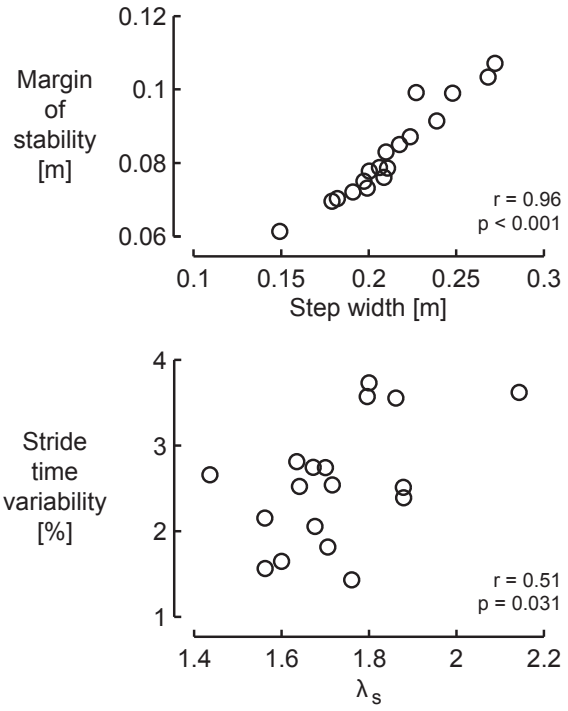

Figure 2: **Several different gait parameters were correlated. A)** Margin of stability and step width were strongly correlated. **B)** Short-term maximum Lyapunov exponent (λ_S) was correlated to stride time variability.

4 Discussion

In this study we aimed to gain more insights into gait stability, gait variability and step width in patients with focal cerebellar lesions. Based on ICARS scores, the patients were only mildly ataxic, and most spatio-temporal gait parameters were similar between groups. When looking at more sensitive gait measures however, group differences could be observed. Gait stability was lower in the patient group (λ_S was higher), and correlated to vermal lesion size ($r = 0.64$; $p = 0.033$), indicating that the patients with the largest lesions in the vermis were the ones with the lowest gait stability. Such a role for vermal regions in gait stability is in line with what was hypothesized based on earlier observations of other gait measures such as step width and stride-to-stride variations [3, 4]. We did not apply more detailed lesion symptom mapping because our patient sample was rather heterogeneous with respect to either ataxia severity (range $0 - 20$) or radiation and chemotherapy history.

Interestingly, while gait stability and step width were different between these mildly ataxic patients and healthy controls, stride time variability was similar between groups. Hence, while on average this patient sample did not show significant deficits in gait variability, their gait stability was impaired. This suggests that, in these mildly ataxic patients, λ_S is a more sensitive measure of gait deficits than gait variability.

In addition to λ_S, we used the margin of stability to assess gait stability [13]. While we expected to see a smaller margin of stability in the patient group, the margin of stability was actually similar between groups, with a tendency to be larger in the patients ($p = 0.08$). However, patients walked with wider steps than healthy controls. The fact that the margin of stability depends on the base of support and the observation that the patient group

walked with wider steps, suggest that step widening could be used as a strategy to ensure a sufficient margin of stability. This is supported by data on amputee gait, as amputees were observed to walk with wider steps than able-bodied controls, with a similar margin of stability [26]. Furthermore, during walking trials with continuous balance perturbations both amputees and able-bodied controls widen their steps in order to increase their margin of stability [27]. Also, when walking backwards, healthy subjects widen their steps and increase their margin of stability [28]. Along this line of reasoning, we argue that the margin of stability and step width should not be used as mutually independent measures to classify gait as stable or instable, as both might or might not have been adapted in situations or populations where balance is challenged. Evaluation of (changes/differences in) step width is needed to interpret margin of stability values appropriately.

A next step to gain more insights into step widening as a compensation strategy could be to evaluate how the relation between step width and the margin of stability changes in cerebellar patients and healthy controls in conditions where normal gait is challenged. Furthermore, only patients in a stable recovery phase were included in the current study (time post-op $4.8 - 30.2$ yr; Table 1). Evaluating the margin of stability in patients in an initial recovery phase could reveal how the nervous system learns to compensate for specific cerebellar-related gait deficits. In addition, alternative compensation strategies should be evaluated in this mildly ataxic patient population as well, since Mari et al. [29] recently identified antagonist muscle co-activation as a potential compensation strategy to reduce imbalance in inherited cerebellar ataxia patients.

In summary, we observed that patients with focal lesions in the cerebellum walked with lower gait stability and wider steps than healthy controls, while other gait parameters were similar. Patients with the largest vermal lesions displayed the least stable gait pattern. These observations in mildly ataxic patients confirm the importance of the cerebellum (and the vermis in particular) in the supraspinal control of gait in humans, specifically in relation to gait stability.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.gaitpost.2015.01.004 and at the end of this document.

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MRI data acquisition and processing

A Philips 3T Achieva MRI scanner (Philips, Best, The Netherlands) with a 32-channel matrix head coil was used for image acquisition. A 3D MPRAGE high resolution T1-weighted image (repetition time = 970ms, echo time = 4.60ms, flip angle = 8º, 230 1-mm slices, in-plane resolution = 0.97×0.98, 384×384 matrix) was acquired for all patients, except #18 (see Table S1).

MRIcroN software (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html) was used to manually trace the lesions on the MPRAGE images. The SUIT toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm [1,2]) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used to spatially normalize the lesion traces to the atlas of the cerebellum [3]. In some cases (large lesions at the outer border of the cerebellum) spatial normalization with the SUIT toolbox was inaccurate. In those cases lesions were spatially normalized based on the whole brain image and the normalized lesions were manually corrected in atlas space when needed, based on the original image. An overlap image of the normalized lesions is presented in Figure S1, an overview of the lesioned lobules of each of the patients is provided in Table S1.

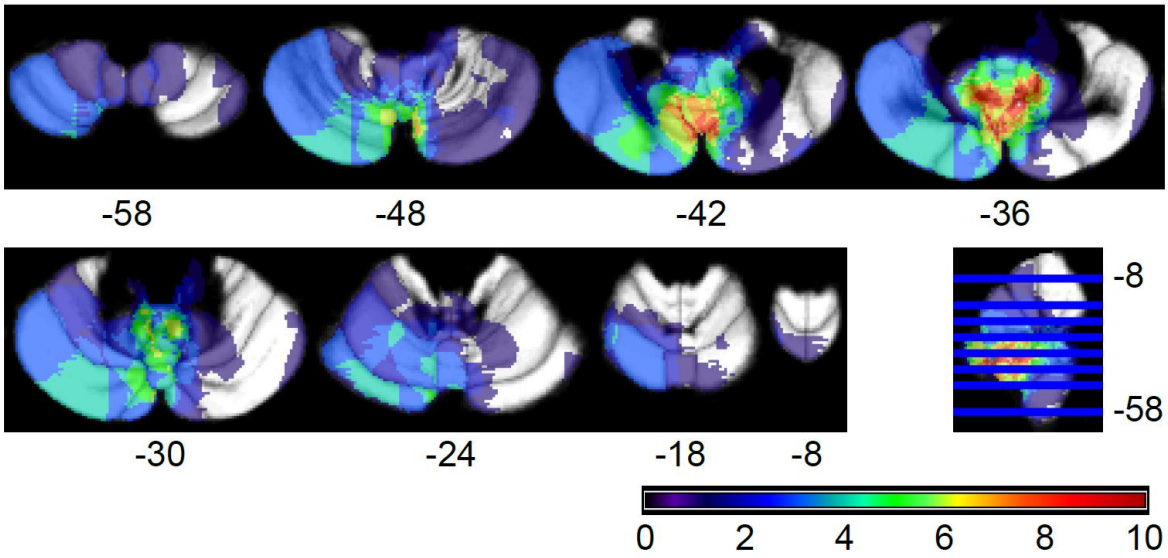

Figure S1. Overlap of lesions normalized to the SUIT template.
Lesion overlap is displayed on 8 axial slices as indicated in the sagital overview slice (bottom right panel). The number of overlapping lesions is indicated by colour code. Maximum overlap (10 patients) was around the border between the left paravermal lobules VIIb and Crus II (color coding according to the heat index below the cerebellar slices).

References:

[1] Diedrichsen J. A spatially unbiased atlas template of the human cerebellum. Neuroimage 2006;33:127–38. doi:10.1016/j.neuroimage.2006.05.056.

[2] Diedrichsen J, Maderwald S, Küper M, Thürling M, Rabe K, Gizewski ER, et al. Imaging the deep cerebellar nuclei: a probabilistic atlas and normalization procedure. Neuroimage 2011;54:1786–94. doi:10.1016/j.neuroimage.2010.10.035.

[3] Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. Neuroimage 2009;46:39–46. doi:10.1016/j.neuroimage.2009.01.045.

Table S1. Overview of lesioned lobules.
Y = yes; L = left; R = right; B = both; FN = fastigial nuclei; IN = interposed nuclei; DN = dentate nuclei

#	Lesion Volume (cm^3)	Vermis								Paravermis										Hemispheres									Nuclei		
		VI	CI	CII	VIIb	VIIIa	VIIIb	IX	X	I-IV	V	VI	CI	CII	VIIb	VIIIa	VIIIb	IX	X	I-IV	V	VI	CI	CII	VIIb	VIIIa	VIIIb	X	FN	IN	DN
1	58.0									L	L	L	L	L	L	L	L			L	L	L	L	L	L	L	L				
2	8.2																						R	R	R	R	R				
3	4.5			Y	Y	Y	Y	Y						L	L	L	L	L												L	
4	1.7															R	R	R	R								R	R			
5	47.3					Y	Y	Y	Y	L	B			B	B	B	B	B						L	L				B	B	B
6	36.3																					L	L	L	L	L					
7	15.7										R	R	R	R	R	R		R				R	R	R	R	R				R	R
8	20.2	Y	Y	Y	Y	Y	Y	Y				B	B	B	B	B	B	B											B	B	
9	58.4											L	L	L	L	L						L	L	L	L	L					
10	2.0	Y	Y	Y	Y	Y	Y							B	R																
11	7.1	Y		Y	Y	Y	Y	Y				R	R	R	B	R	R	R												R	B
12	8.6					Y	Y	Y	Y						R	R	R	B	R										R	R	
13	22.0					Y	Y	Y	Y	L	B			B	B	B	B	B							L	L			B	B	B
14	6.3					Y	Y	Y	Y					R	R	R	R	B												R	B
15	5.4	Y		Y	Y	Y	Y	Y	Y					B	B			B											R	B	B
16	14.2	Y		Y	Y	Y	Y	Y	Y	B	B			B	B	B	B	B											B	B	B
17	22.6	Y	Y	Y	Y	Y	Y	Y		B	B	L	L	B	B	B	B	B			L	L							B	L	B
18	no MRI																														